Bacteriophage Inhibits Metastasis in Mouse Transplantable Melanoma Model

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Bacteriophages (BP) are viruses that infect, multiply within, and cause lysis of bacterial cells. Recently, there has been renewed interest in the use of BP in the treatment of patients with severe bacterial infections, especially those which are antibiotic resistant. The first suggestion that BP may have anticancer activities stems from observations made by Bloch in 1940 (1). He showed that BP can almost selectively accumulate in cancer tissue and eventually inhibit the growth of tumors. These results were confirmed by scientists from our Institute who demonstrated that cancer cells bind BP in vitro (2).

With these data in mind, we turned our attention to the potential anticancer effects of BP administration and decided to study this phenomenon in a mouse transplantable melanoma model. From the large array of bacteriophage strains, we choose an E.coli-specific phage – T4. Moreover, by consecutive passages in vitro on B16 cells, we selected the T4 substrain HAP1, with high affinity to B16 melanoma cells. The BP were used in the form of lysates obtained after the culture of BP with Escherichia coli B. BP concentration in the lysates was 1-2 x 10^9 pfu/ml.

C57Bl/6 mice were injected intravenously (lateral tail vein) with 3 x 10^5 B16 cells in 0.2 ml of physiological saline. The intraperitoneal treatment (0.2 ml/mouse, thus 0.2-0.4 x 10^9 pfu/mouse) was started 1 hour before tumor cell inoculation and continued daily until the end of the experiment (21-22 days).

Two groups of mice served as an experimental control: a) mice injected with 0.9% NaCl; and b) mice injected with a sonificated Escherichia coli B culture, with LPS concentration comparable to that of the lysates of BP.

A marked and statistically significant inhibition of tumor lung colony formation was observed both in mice treated with T4 phage and with NHAP1 (48 and 80%, respectively). Moreover, HAP1 caused a significantly higher inhibition of tumor growth than the parental T4 phage. In vitro experiments revealed no effect of either phage on the proliferation of B16 melanoma cells. It should be stressed that no toxic side effects of the applied treatment were observed.

Recent data strongly suggest an important role of cancer- and endothelial-cello β3 integrins in tumor expansion and metastasis. Interestingly, T4 phage protein 24 contains a KGD tripeptide sequence (also present in collagen) which is a ligand for that integrin. Moreover, in a region preceding the KGD tripeptide there is a slight homology of the protein 24 to mouse collagen (Mouse Genome Informatics). Thus, we hypothesize that the Bacteriophage can bind cancer/endothelial integrin (αIIbβ3 and perhaps αvβ3, which is also used by other viruses) and thereby inhibit tumor-endothelial cell interactions. Furthermore, BP protein 24 could inhibit tumor cell attachment to collagen.

To the best of our knowledge, this is the first observation of the antimetastatic activity of BP. We believe that the preliminary observations reported herein deserve further study to determine the potential anticancer activity of BP.